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Solitary Focal Demyelination in the Brain as a Paraneoplastic Disorder

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Solitary focal demyelination (SFD) in the brain is an uncommon and poorly understood disorder of uncertain etiology that may represent an intermediate entity between multiple sclerosis and acute disseminated encephalomyelitis. In a few reported cases of SFD, the patient was briefly noted to have a nonneurological malignancy.

We studied two patients who had solitary focal lesions in the brain. Utilizing magnetic resonance imaging and tissue biopsy, we found the characteristics of the brain lesions in these two patients to be those of SFD. In our combined experience over the past 10 years, we have encountered no similar brain lesions at our medical center. We found it remarkable that both of these patients also had malignancy outside of the nervous system. One had a seminoma, and the other a lymphoma. We conclude that some cases of SFD in the brain may occur as a paraneoplastic disorder associated with nonneurological malignancies.

Key words: brain, demyelination, paraneoplastic

INTRODUCTION

Demyelination in the brain is frequently caused by multiple sclerosis (MS), although other infectious, metabolic, and autoimmune etiologies are well recognized [1–5]. Solitary focal demyelination (SFD) in the brain is an uncommon and poorly understood disorder of uncertain pathogenesis [1–5] that may represent an intermediate entity between multiple sclerosis and acute disseminated encephalomyelitis [6]. The appearance of SFD on imaging frequently resembles a tumor, with mass effect, contrast enhancement, and extension across the corpus callosum suggesting a butterfly glioma [1–4,6]. Here, we report SFD in two patients who had malignancies outside of the nervous system.

PATIENT 1

A 41-year-old male, previously healthy, was hospitalized after 1 month of worsening depression and difficulty with concentration and memory. Physical examination revealed him to be alert but oriented only to person and place. He had a right homonymous hemianopsia and mild clumsiness in both hands.

Magnetic resonance imaging (MRI) revealed a solitary mass lesion involving both occipital lobes and the corpus callosum, with decreased signal on T1-weighted images and increased signal on proton density (Fig. 1) and T2-weighted images. It exhibited some peripheral contrast enhancement and edema. Cerebrospinal fluid (CSF) was normal except for a protein of 156 mg/dl. The CSF IgG index and the myelin basic protein were both normal. There was no evidence of oligoclonal banding.

An open biopsy of the brain lesion revealed a sharply demarcated lesion that was confined to the white matter and was characterized by loss of oligodendroglia, the diffuse infiltration of macrophages, and reactive astrocytosis (Fig. 2A). Myelin was absent within the lesion (Fig. 2B), whereas axons were relatively preserved (Fig. 2C). Perivascular cuffs of lymphocytes were noted around some of the vessels within the area of myelin loss (Fig. 2D). The cortex was spared. No microorganisms, viral inclusion bodies, or abnormal glial cells were seen. These findings taken together were consistent with a demyelinating disorder.

The patient improved significantly following a brief course of oral corticosteroid therapy, but he returned 2 months later complaining of abdominal pain. Workup

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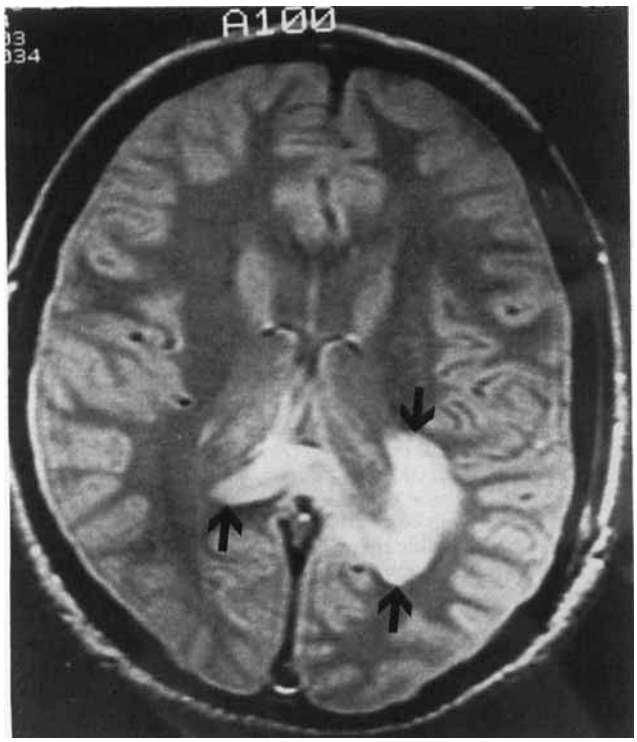

Fig. 1. MRI of brain, Patient 1. A well-demarcated area of increased signal (arrows) on an axial proton density image involves both occipital lobes and the corpus callosum, completely sparing the cerebral cortex.

revealed a retroperitoneal seminoma (Fig. 3). Anti-Hu, anti-Yo, and anti-Ri antibodies were absent in the patient's serum. Now 5 years later, status post surgery and chemotherapy, he is considered to be cured of his seminoma. He has experienced remarkable neurological improvement, both clinically and radiographically, with no occurrence of new CNS lesions. This patient's initial presentation was briefly described by Kepes [6] in a series of 24 patients having SFD in the brain.

PATIENT 2

A 70-year-old white male was brought to medical attention by his wife who complained that he had recently become confused and inattentive. The past medical history was remarkable only for malignant lymphoma, nodular poorly differentiated lymphocytic type, diagnosed 4 years earlier and treated at various times with chlorambucil, prednisone, and mitoxantrone. Physical examination revealed him to be alert, but oriented only to person and place. He had mild weakness of the right face and arm.

MRI revealed involvement of both frontal lobes and the corpus callosum by a solitary mass lesion that was nonenhancing with decreased signal on T1-weighted images and increased signal on proton density (Fig. 4) and T2-weighted images. A stereotactic biopsy (Fig. 5) revealed reactive astrocytosis and prominent foamy histiocytes with myelin debris within the histiocyte cytoplasm. Axons were relatively preserved. No lymphoma cells, microorganisms, viral inclusion bodies, or abnormal glial cells were seen. These findings taken together were consistent with a demyelinating disorder. Testing for antineuronal antibodies was not done.

The patient refused further evaluation and treatment. Three months later he died and his family refused an autopsy.

DISCUSSION

We have described two patients who experienced neurological symptoms associated with nonneurological malignancy. Imaging of these patients revealed solitary focal mass lesions in the brain that were similar in signal characteristics. Each patient underwent biopsy of his brain lesion, and the histology in each case revealed demyelination with no evidence of malignancy or progressive multifocal leukoencephalopathy. In our combined experience over the past 10 years, we have encountered no similar brain lesions at our medical center. We found it remarkable that each of these patients also had malignancy outside of the nervous system, and since our only experience with SFD in the brain has occurred in the setting of nonneurological malignancy, we conclude that some cases of SFD in the brain may occur as a paraneoplastic disorder.

The brain lesions in our two cases of SFD are similar to those described in previous cases [1–6], reported by most authors [1–5] to be of uncertain pathogenesis. Kepes [6] recently described 24 patients with SFD in the brain and considered them possibly to represent an intermediate entity between MS and acute disseminated encephalomyelitis. It is of interest that four of these 24 patients had malignancies: three were nonneurological (cases 12, 24, 27), and one was a brain malignancy (case 14). These cases lend further support to our conclusion that some cases of SFD in the brain may occur as a paraneoplastic disorder.

Paraneoplastic demyelination in the central nervous system (CNS) only occasionally has been implied in previous reports and has not been limited to focal lesions of the brain. Kuroda et al. [7] described paraneoplastic necrotizing myelopathy in a patient with markedly elevated myelin basic protein suggesting a process similar to MS. At autopsy severe demyelination and necrosis were found to involve the optic chiasm, the medulla, and the entire spinal cord. Papillary carcinoma of the thyroid gland was an incidental finding at autopsy, and no metastases were identified. The authors suggested "the possibility of autoimmune demyelination for the pathogenesis of paraneoplastic acute necrotizing myelopathy." This case of pos-

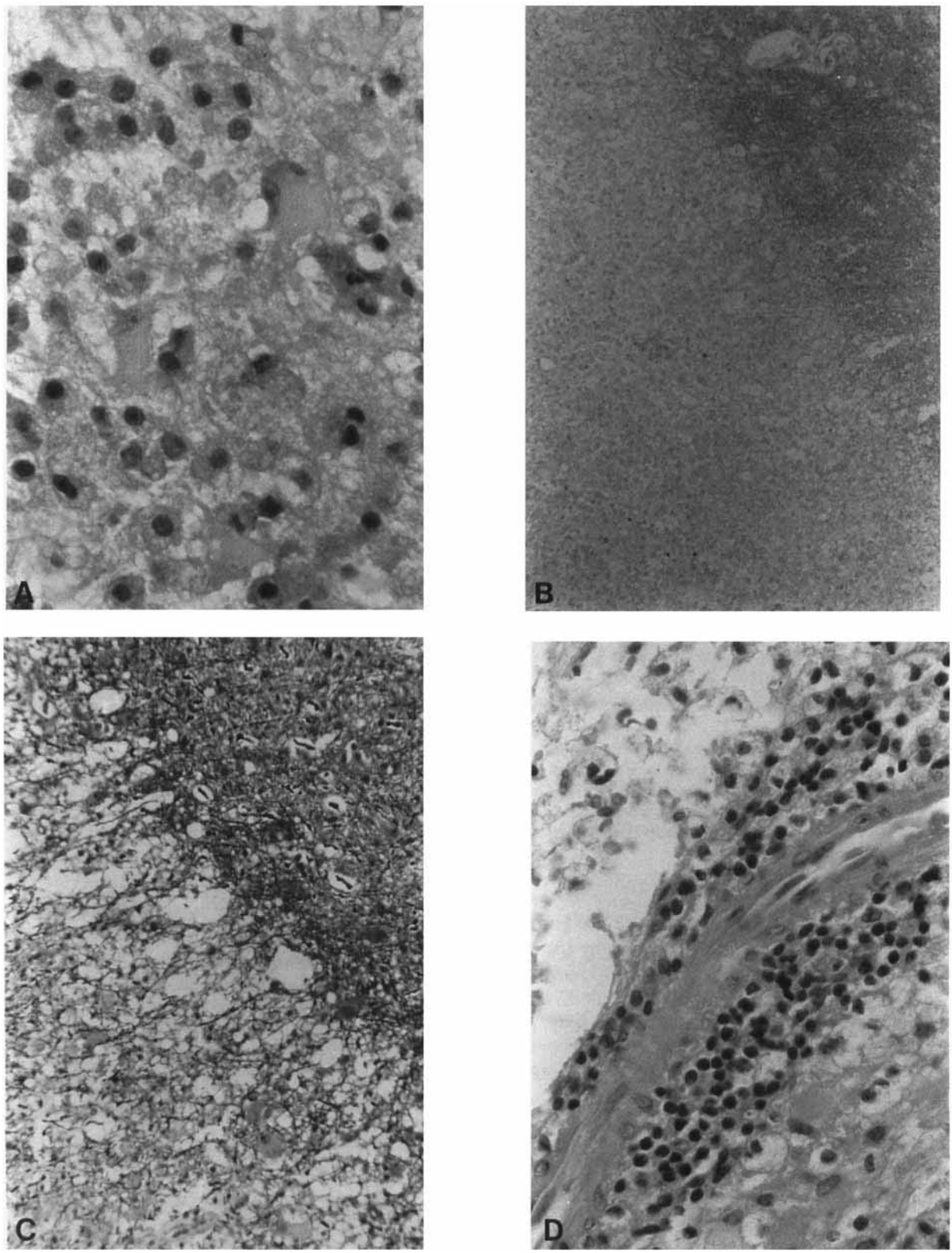

Fig. 2. White matter lesion, Patient 1. **A.** Infiltration of macrophages with reactive astrocytosis. (H&E, original magnification ×750). **B.** Border of lesion showing myelin loss in lesion with preserved myelin in adjacent brain (Luxol fast blue/PAS, original magnification ×100). **C.** Border of lesion showing preserved axons in lesion, although there is some loss when compared to adjacent brain (Bielschowsky, original magnification ×200). **D.** Perivascular cuff of lymphocytes in lesion (H&E, original magnification ×600).

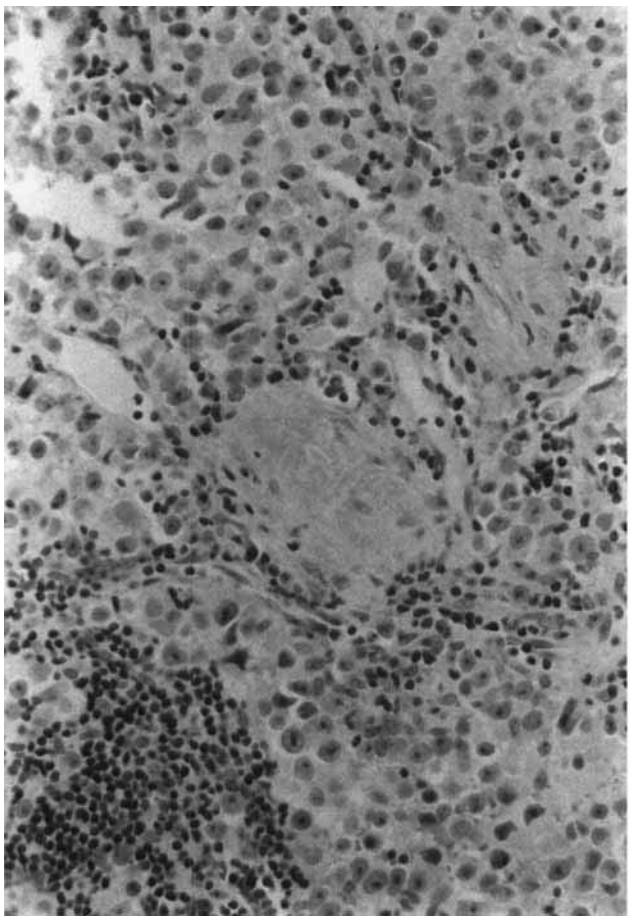

Fig. 3. Seminoma, Patient 1. Histology of retroperitoneal mass demonstrating typical findings of seminoma with large tumor cells having abundant cytoplasm, large nuclei, and prominent nucleoli. As is characteristic of seminoma, septa of fibrous tissue and collections of lymphocytes are interspersed among the tumor cells (H&E, original magnification ×300).

Fig. 4. MRI of brain, Patient 2. A well-demarcated area of increased signal (arrows) on an axial proton density image involves both frontal lobes and the corpus callosum, apparently sparing the cerebral cortex.

sible paraneoplastic CNS demyelination differs from ours by being multifocal rather than focal and by including areas of necrosis. Glantz et al. [8] described four patients who had various paraneoplastic lesions of the CNS. Although only two of their four cases underwent biopsy, the histopathology of one of their cases, a paraneoplastic myelopathy (case 3), was consistent with demyelination. This finding again suggests that paraneoplastic demyelination may occur in the spinal cord.

SFD may cause difficulty in diagnosis. It often presents clinically and radiographically as a tumor with the correct diagnosis being discovered only after the biopsy reveals demyelinated white matter. MS may then enter into the differential diagnosis, and although its protean nature may generate nosologic ambiguity [6], it is typically distinguishable from SFD by its tendency to be multifocal with recurrent exacerbations and remissions.

There is some uncertainty regarding the optimal treatment for SFD. Although many reported cases have responded to oral corticosteroids [6] as did our Patient 1, too few patients have been treated with other immunosuppressive therapies for the efficacy of these to be assessed. The importance of early recognition of SFD may lie in the recognition and treatment of an associated nonneurological malignancy. In the case of our Patient 1, we found paraneoplastic SFD to occur in association with a curable malignancy.

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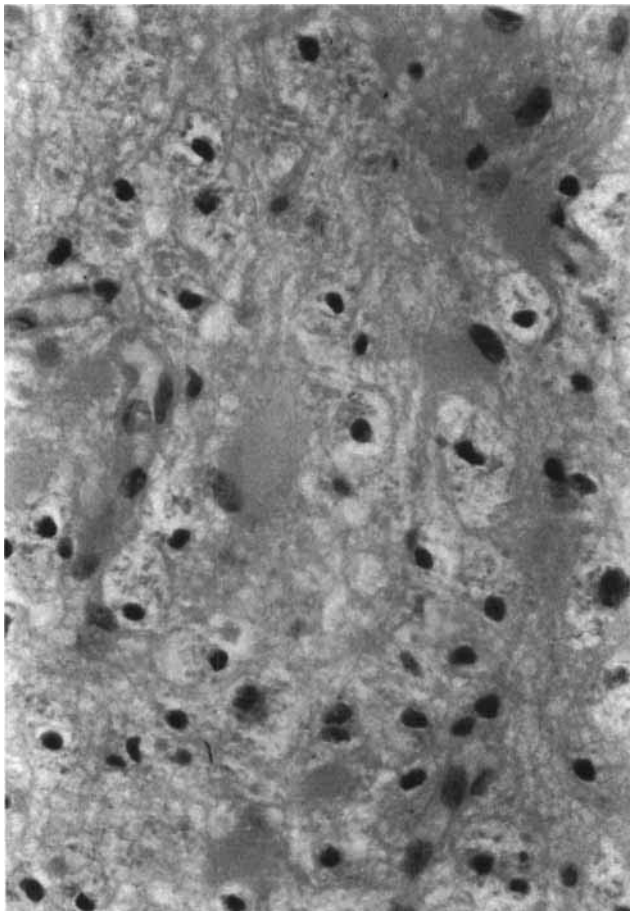

Fig. 5. White matter lesion, Patient 2. Reactive gliosis, and prominent foamy histiocytes with myelin debris within the histiocyte cytoplasm (Luxol fast blue/H&E, original magnification ×660).

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